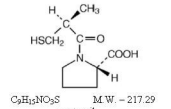
CAPTOPRIL AND HYDROCHLOROTHIAZIDE - captopril and hydrochlorothiazide tablet
Endo Pharmaceuticals Inc.

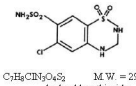
USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Captopril and Hydrochlorothiazide should be discontinued as soon as possible. See WARNINGS: Captopril, Fetal/Neonatal Morbidity and Mortality.

DESCRIPTION

Captopril and hydrochlorothiazide are two oral antihypertensive agents. Captopril, the first of a new class of antihypertensive agents, is a specific competitive inhibitor of angiotensin I-converting enzyme (ACE), the enzyme responsible for the conversion of angiotensin I to angiotensin II. Hydrochlorothiazide is a benzothiadiazide (thiazide) diuretic-antihypertensive.
Captopril is a white to off-white crystalline powder that may have a slight sulfurous odor; it is soluble in water (approx. 160 mg/mL), methanol, and ethanol and sparingly soluble in chloroform and ethyl acetate.
Hydrochlorothiazide is a white crystalline powder slightly soluble in water but freely soluble in sodium hydroxide solution.
Captopril is designated chemically as 1-[(2S)-3-Mercapto-2-methylpropionyl]-L-proline; hydrochlorothiazide is 6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Their structural formulas are:



$C_9H_{15}NO_3S$ M.W. = 217.29
captopril



$C_7H_8ClN_3O_4S_2$ M.W. = 297.75
hydrochlorothiazide

Each tablet, for oral administration, contains captopril and hydrochlorothiazide, 25 mg/15 mg, 25 mg/25 mg, 50 mg/15 mg, or 50 mg/25 mg. In addition, each tablet contains the following inactive ingredients: lactose monohydrate, magnesium stearate, microcrystalline cellulose, pregelatinized starch and stearic acid. In addition, colorant (FD&C Yellow No. 6) is contained in the 25 mg/25 mg and 50 mg/25 mg tablets.

CLINICAL PHARMACOLOGY

Captopril

Mechanism of Action
The mechanism of action of captopril has not yet been fully elucidated. Its beneficial effects in hypertension and heart failure appear to result primarily from suppression of the renin-angiotensin-aldosterone system. However, there is no consistent correlation between renin levels and response to the drug. Renin, an enzyme synthesized by the kidneys, is released into the circulation where it acts on a plasma globulin substrate to produce angiotensin I, a relatively inactive decapeptide. Angiotensin I is then converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent endogenous vasoconstrictor substance. Angiotensin II also stimulates aldosterone secretion from the adrenal cortex, thereby contributing to sodium and fluid retention.

Captopril prevents the conversion of angiotensin I to angiotensin II by inhibition of ACE, a peptidyldipeptide carboxy hydrolase. This inhibition has been demonstrated in both healthy human subjects and in animals by showing that the elevation of blood pressure caused by exogenously administered angiotensin I was attenuated or abolished by captopril. In animal studies, captopril did not alter the pressor responses to a number of other agents, including angiotensin II and norepinephrine, indicating specificity of action.

ACE is identical to“bradykininase”, and captopril may also interfere with the degradation of the vasodepressor peptide, bradykinin. Increased concentrations of bradykinin or prostaglandin E_2 may also have a role in the therapeutic effect of captopril.

Inhibition of ACE results in decreased plasma angiotensin II and increased plasma renin activity (PRA), the latter resulting from loss of negative feedback on renin release caused by reduction in angiotensin II. The reduction of angiotensin II leads to decreased aldosterone secretion, and, as a result, small increases in serum potassium may occur along with sodium and fluid loss.

The antihypertensive effects persist for a longer period of time than does demonstrable inhibition of circulating ACE. It is not known whether the ACE present in vascular endothelium is inhibited longer than the ACE in circulating blood.

Pharmacokinetics
After oral administration of therapeutic doses of captopril, rapid absorption occurs with peak blood levels at about one hour. The presence of food in the gastrointestinal tract reduces absorption by about 30 to 40 percent; captopril therefore should be given one hour before meals. Based on carbon-14 labeling, average minimal absorption is approximately 75 percent. In a 24-hour period, over

95 percent of the absorbed dose is eliminated in the urine; 40 to 50 percent is unchanged drug; most of the remainder is the disulfide dimer of captopril and captopril-cysteine disulfide.

Approximately 25 to 30 percent of the circulating drug is bound to plasma proteins. The apparent elimination half-life for total radioactivity in blood is probably less than three hours. An accurate determination of half-life of unchanged captopril is not, at present, possible, but it is probably less than two hours. In patients with renal impairment, however, retention of captopril occurs (see DOSAGE AND ADMINISTRATION).

Pharmacodynamics
Administration of captopril results in a reduction of peripheral arterial resistance in hypertensive patients with either no change, or an increase, in cardiac output. There is an increase in renal blood flow following administration of captopril and glomerular filtration rate is usually unchanged. In patients with heart failure, significantly decreased peripheral (systemic vascular) resistance and blood pressure (afterload), reduced pulmonary capillary wedge pressure (preload) and pulmonary vascular resistance, increased cardiac output, and increased exercise tolerance time (ETT) have been demonstrated.

Reductions of blood pressure are usually maximal 60 to 90 minutes after oral administration of an individual dose of captopril. The duration of effect is dose related and is extended in the presence of a thiazide-type diuretic. The full effect of a given dose may not be attained for 6 to 8 weeks (see DOSAGE AND ADMINISTRATION). The blood pressure lowering effects of captopril and thiazide-type diuretics are additive. In contrast, captopril and beta-blockers have a less than additive effect.

Blood pressure is lowered to about the same extent in both standing and supine positions. Orthostatic effects and tachycardia are infrequent but may occur in volume-depleted patients. Abrupt withdrawal of captopril has not been associated with a rapid increase in blood pressure.

Studies in rats and cats indicate that captopril does not cross the blood-brain barrier to any significant extent.

Hydrochlorothiazide
Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.
Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate.
The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.
The mean plasma half-life of hydrochlorothiazide in fasted individuals has been reported to be approximately 2.5 hours.
Onset of diuresis occurs in two hours and the peak effect at about four hours. Its action persists for approximately six to twelve hours.
Hydrochlorothiazide is eliminated rapidly by the kidney.

INDICATIONS AND USAGE
Captopril and Hydrochlorothiazide tablets are indicated for the treatment of hypertension. The blood pressure lowering effects of captopril and thiazides are approximately additive.
This fixed combination drug may be used as initial therapy or substituted for previously titrated doses of the individual components. When captopril and hydrochlorothiazide are given together it may not be necessary to administer captopril in divided doses to attain blood pressure control at trough (before the next dose). Also, with such a combination, a daily dose of 15 mg of hydrochlorothiazide may be adequate.
Treatment may, therefore, be initiated with Captopril and Hydrochlorothiazide tablets 25 mg/15 mg once daily. Subsequent titration should be with additional doses of the components (captopril, hydrochlorothiazide) as single agents or as Captopril and Hydrochlorothiazide tablets 50 mg/15 mg, 25 mg/25 mg, or 50 mg/25 mg (see DOSAGE AND ADMINISTRATION).
In using Captopril and Hydrochlorothiazide tablets, consideration should be given to the risk of neutropenia/agranulocytosis (seeWARNINGS).
Captopril and Hydrochlorothiazide tablets may be used for patients with normal renal function, in whom the risk is relatively low. In patients with impaired renal function, particularly those with collagen vascular disease, Captopril and Hydrochlorothiazide tablets should be reserved for hypertensives who have either developed unacceptable side effects on other drugs, or have failed to respond satisfactorily to other drug combinations.
ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (seeWARNINGS: Angioedema).

CONTRAINDICATIONS

Captopril
This product is contraindicated in patients who are hypersensitive to captopril or any other angiotensin-converting enzyme inhibitor (e.g., a patient who has experienced angioedema during therapy with any other ACE inhibitor).

Hydrochlorothiazide
Hydrochlorothiazide is contraindicated in anuria. It is also contraindicated in patients who have previously demonstrated hypersensitivity to hydrochlorothiazide or other sulfonamide-derived drugs.

WARNINGS

Captopril

Anaphylactoid and Possibly Related Reactions
Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including Captopril and Hydrochlorothiazide tablets) may be subject to a variety of adverse reactions, some of them serious.

Angioedema
Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been seen in patients treated with ACE inhibitors, including captopril. If angioedema involves the tongue, glottis or larynx, airway obstruction may occur and be fatal. Emergency therapy, including but not necessarily limited to, subcutaneous administration of a 1:1000 solution of epinephrine should be promptly instituted.

Swelling confined to the face, mucous membranes of the mouth, lips and extremities has usually resolved with discontinuation of treatment; some cases required medical therapy. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS: Captopril.)

Anaphylactoid reactions during desensitization
Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.

Anaphylactoid reactions during membrane exposure
Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Neutropenia/Agranulocytosis
Neutropenia ($<1000/mm^3$) with myeloid hypoplasia has resulted from use of captopril. About half of the neutropenic patients developed systemic or oral cavity infections or other features of the syndrome of agranulocytosis.

The risk of neutropenia is dependent on the clinical status of the patient:

In clinical trials in patients with hypertension who have normal renal function (serum creatinine less than 1.6 mg/dL and no collagen vascular disease), neutropenia has been seen in one patient out of over 8,600 exposed.

In patients with some degree of renal failure (serum creatinine at least 1.6 mg/dL) but no collagen vascular disease, the risk of neutropenia in clinical trials was about 1 per 500, a frequency over 15 times that for uncomplicated hypertension. Daily doses of captopril were relatively high in these patients, particularly in view of their diminished renal function. In foreign marketing experience in patients with renal failure, use of allopurinol concomitantly with captopril has been associated with neutropenia but this association has not appeared in U.S. reports.

In patients with collagen vascular diseases (e.g., systemic lupus erythematosus, scleroderma) and impaired renal function, neutropenia occurred in 3.7 percent of patients in clinical trials.

While none of the over 750 patients in formal clinical trials of heart failure developed neutropenia, it has occurred during the subsequent clinical experience. About half of the reported cases had serum creatinine ≥1.6 mg/dL and more than 75 percent were in patients also receiving procainamide. In heart failure, it appears that the same risk factors for neutropenia are present.

The neutropenia has usually been detected within three months after captopril was started. Bone marrow examinations in patients with neutropenia consistently showed myeloid hypoplasia, frequently accompanied by erythroid hypoplasia and decreased numbers of megakaryocytes (e.g., hypoplastic bone marrow and pancytopenia); anemia and thrombocytopenia were sometimes seen.

In general, neutrophils returned to normal in about two weeks after captopril was discontinued, and serous infections were limited to clinical complex patients. About 13 percent of the cases of neutropenia have ended fatally, but almost all fatalities were in patients

with serious illness, having collagen vascular disease, renal failure, heart failure or immunosuppressant therapy, or a combination of these complicating factors.

Evacuation of the hypertensive or heart failure patient should always include assessment of renal function.

If captopril is used in patients with impaired renal function, white blood cell and differential counts should be evaluated prior to starting treatment and at approximately two-week intervals for about three months, then periodically.

In patients with collagen vascular disease or who are exposed to other drugs known to affect the white cells or immune response, particularly when there is impaired renal function, captopril should be used only after assessment of benefit and risk, and then with caution.

All patients treated with captopril should be told to report any signs of infection (e.g., sore throat, fever). If infection is suspected, white cell counts should be performed without delay.

Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophils count $<1000/mm^3$) the physician should withdraw captopril and closely follow the patient's course.

Proteinuria
Total urinary proteins greater than 1 g per day were seen in about 0.7 percent of patients receiving captopril. About 90 percent of affected patients had evidence of prior renal disease or received relatively high doses of captopril (in excess of 150 mg/day), or both. The nephrotic syndrome occurred in about one-fifth of proteinuric patients. In most cases, proteinuria subsided or cleared within six months whether or not captopril was continued. Parameters of renal function, such as BUN and creatinine, were seldom altered in the patients with proteinuria.

Hypotension
Excessive hypotension was rarely seen in hypertensive patients but is a possible consequence of captopril use in salt/volume depleted persons (such as those treated vigorously with diuretics), patients with heart failure or those patients undergoing renal dialysis. (See PRECAUTIONS: Drug Interactions.)

Fetal/Neonatal Morbidity and Mortality
ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to the ACE-inhibitor exposure.

These adverse effects do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to ACE inhibitors only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of captopril as soon as possible.

Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, captopril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as a means of reversing hypotension and/or substituting for disordered renal function. While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

When captopril was given to rabbits at doses about 0.8 to 70 times (on a mg/kg basis) the maximum recommended human dose, low incidences of craniofacial malformations were seen. N0 teratogenic effects of captopril were seen in studies of pregnant rats and hamsters. On a mg/kg basis, the doses used were up to 150 times (in hamsters) and 625 times (in rats) the maximum recommended human dose.

Hepatic Failure
Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

Hydrochlorothiazide
Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
In general, lithium should not be given with diuretics (see PRECAUTIONS: Drug Interactions, Hydrochlorothiazide).

PRECAUTIONS

General

Captopril

Impaired Renal Function
Some patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine after reduction of blood pressure with captopril. Captopril dosage reduction and/or discontinuation of diuretic may be required. For some of these patients, it may not be possible to normalize blood pressure and maintain adequate renal perfusion (see CLINICAL PHARMACOLOGY, DOSAGE AND ADMINISTRATION,ADVERSE REACTIONS: Altered Laboratory Findings).

Hyperkalemia
Elevations in serum potassium have been observed in some patients treated with ACE inhibitors, including captopril. When treated with ACE inhibitors, patients at risk for the development of hyperkalemia include those with: renal insufficiency; diabetes mellitus; and those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or other drugs associated with increases in serum potassium. (See PRECAUTIONS: Information for Patients and Drug Interactions, Captopril;ADVERSE REACTIONS: Altered Laboratory Findings.)

Cough
Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough.

Surgery/Anesthesia
In patients undergoing major surgery or during anesthesia with agents that produce hypotension, captopril will block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it can be corrected by volume exposure.

Hemodialysis
Recent clinical observations have shown an association of hypersensitivity-like (anaphylactoid) reactions during hemodialysis with high-flux dialysis membranes (e.g., AN69) in patients receiving ACE inhibitors as medication. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of medication. (See WARNINGS: Captopril: Anaphylactoid reactions during membrane exposure.)

Hydrochlorothiazide
Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance may include: dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Hypokalemia may develop, especially with brisk diuresis, or when severe cirrhosis is present. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Because captopril reduces the production of aldosterone, concomitant therapy with captopril reduces the diuretic-induced hypokalemia. Fewer patients may require potassium supplements and/or foods with a high potassium content (see Drug Interactions, Agents Increasing Serum Potassium).

Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.

Latent diabetes mellitus may become manifest during thiazide administration.

The antihypertensive effect of thiazide diuretics may be enhanced in the postsympathectomy patient.

If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen (BUN), a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.

Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Information for Patients
Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (e.g., swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See WARNINGS: Captopril: Angioedema.)
Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.
All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.
Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physicians. (See PRECAUTIONS: General and Drug Interactions, Captopril; ADVERSE REACTIONS: Captopril.)
Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.
Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.
Patients should be informed that Captopril and Hydrochlorothiazide tablets should be taken one hour before meals (see DOSAGE AND ADMINISTRATION).

Pregnancy
Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors, and they should also be told that these consequences do not appear to have resulted from intrauterine ACE-inhibitor exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Laboratory Tests
Serum electrolyte levels should be regularly monitored (see WARNINGS: Captopril and Hydrochlorothiazide; PRECAUTIONS: General, Hydrochlorothiazide).

Drug Interactions

Captopril

Hypotension – Patients on Diuretic Therapy
Patients on diuretics and especially those in whom diuretic therapy was recently instituted, as well as those on severe dietary salt restriction or dialysis, may occasionally experience a precipitous reduction of blood pressure usually within the first hour after receiving the initial dose of captopril.

The possibility of hypotensive effects with captopril can be minimized by either discontinuing the diuretic or increasing the salt intake approximately one week prior to initiation of treatment with captopril or initiating therapy with small doses (6.25 or 12.5 mg). Alternatively, provide medical supervision for at least one hour after the initial dose. If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of normal saline. This transient hypotensive response is not a contraindication to further doses which can be given without difficulty once the blood pressure has increased after volume expansion.

Agents Having Vasodilator Activity
Data on the effect of concomitant use of other vasodilators in patients receiving captopril for heart failure are not available; therefore, nitroglycerin or other nitrates (as used for management of angina) or other drugs having vasodilator activity should, if possible, be discontinued before starting captopril. If resumed during captopril therapy, such agents should be administered cautiously, and perhaps at lower dosage.

Agents Causing Renin Release
Captopril's effect will be augmented by antihypertensive agents that cause renin release. For example, diuretics (e.g., thiazides) may activate the renin-angiotensin-aldosterone system.

Agents Affecting Sympathetic Activity
The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Therefore, agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) should be used with caution. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive.

Agents Increasing Serum Potassium
Since captopril decreases aldosterone production, elevation of serum potassium may occur. Potassium-sparing diuretics such as spironolactone, triamterene, or amiloride, or potassium supplements, should be given only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium. Salt substitutes containing potassium should also be used with caution.

Inhibitors Of Endogenous Prostaglandin Synthesis
It has been reported that indomethacin may reduce the antihypertensive effect of captopril, especially in cases of low renin hypertension. Other nonsteroidal anti-inflammatory agents (e.g., aspirin) may also have this effect.

Lithium
Increased serum lithium levels and symptoms of lithium toxicity have been reported in patients receiving concomitant lithium and ACE inhibitor therapy. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended. If a diuretic is also used, it may increase the risk of lithium toxicity (seePRECAUTIONS: Drug Interactions, Hydrochlorothiazide, Lithium).

Hydrochlorothiazide
When administered concurrently the following drugs may interact with thiazide diuretics:

Alcohol, barbiturates, or narcotics –
potentiation of orthostatic hypotension may occur.

Amphotericin B, corticosteroids, or corticotrophin (ACTH) –
may intensify electrolyte imbalance, particularly hypokalemia. Monitor potassium levels; use potassium replacements if necessary.

Anticoagulants (oral) –
dosage adjustments of anticoagulant medication may be necessary since hydrochlorothiazide may decrease their effects.

Antigout medications –
dosage adjustments of antigout medication may be necessary since hydrochlorothiazide may raise the level of blood uric acid.

Other antihypertensive medications (e.g., ganglionic or peripheral adrenergic blocking agents)–
dosage adjustments may be necessary since hydrochlorothiazide may potentiate their effects.

Antidiabetic drugs (oral agents and insulin)–
since thiazides may elevate blood glucose levels, dosage adjustments of antidiabetic agents may be necessary.

Calcium salts –
increased serum calcium levels due to decreased excretion may occur. If calcium must be prescribed monitor serum calcium levels and adjust calcium dosage accordingly.

Cardiac glycosides –
enhanced possibility of digitalis toxicity associated with hypokalemia. Monitor potassium levels (see PRECAUTIONS: Drug Interactions, Captopril).

Cholestyramine and colestipol resins –
absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85 and 43 percent, respectively.

Diazoxide –
enhanced hyperglycemic, hyperuricemic, and antihypertensive effects. Be cognizant of possible interaction; monitor blood glucose and serum uric acid levels.

Lithium –
diuretic agents reduce the renal clearance of lithium and increase the risk of lithium toxicity. These drugs should be coadministered with caution and frequent monitoring of serum lithium levels is recommended (see PRECAUTIONS: Drug Interactions, Captopril, Lithium).

MAO inhibitors –
dosage adjustments of one or both agents may be necessary since hypotensive effects are enhanced.

Nondepolarizing muscle relaxants, preanesthetics and anesthetics used in surgery (e.g., tubocurarine chloride and gallamine triethiodide) –
effects of these agents may be potentiated; dosage adjustments may be required. Monitor and correct any fluid and electrolyte imbalances prior to surgery if feasible.

Nonsteroidal anti-inflammatory agents –
in some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing or thiazide diuretics. Therefore, when hydrochlorothiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Methenamine –
possible decreased effectiveness due to alkalinization of the urine.

Pressor amines (e.g., norepinephrine) –
decreased arterial responsiveness, but not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Use caution in patients taking both medications who undergo surgery. Administer preanesthetic and anesthetic agents in reduced dosage, and if possible, discontinue hydrochlorothiazide therapy one week prior to surgery.

Probenecid or sulfinpyrazone –
increased dosage of these agents may be necessary since hydrochlorothiazide may have hyperuricemic effects.

Drug/Laboratory Test Interactions

Captopril
Captopril may cause a false-positive urine test for acetone.

Hydrochlorothiazide
Hydrochlorothiazide may cause diagnostic interference of the bentiromide test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Captopril
Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential.

Studies in rats have revealed no impairment of fertility.

Hydrochlorothiazide
Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Hydrochlorothiazide was not genotoxic in *in vitro* assays using strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 of*Salmonella typhimurium* (Ames assay) and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations, or*in vivo assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes, and the Drosophila* sex linked recessive lethal trait gene. Positive test results were obtained only in the*in vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 13μg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration.

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Animal Toxicology
Captopril
Chronic oral toxicity studies were conducted in rats (2 years), dogs (47 weeks; 1 year), mice (2 years), and monkeys (1 year). Significant drug-related toxicity included effects on hematopoiesis, renal toxicity, erosion/ulceration of the stomach, and variation of retinal blood vessels.
Reductions in hemoglobin and/or hematocrit values were seen in mice, rats, and monkeys at doses 50 to 150 times the maximum recommended human dose (MRHD). Anemia, leukopenia, thrombocytopenia, and bone marrow suppression occurred in dogs at doses 8 to 30 times MRHD. The reductions in hemoglobin and hematocrit values in rats and mice were only significant at 1 year and returned to normal with continued dosing by the end of the study. Marked anemia was seen at all dose levels (8 to 30 times MRHD) in dogs, whereas moderate to marked leukopenia was noted only at 15 and 30 times MRHD and thrombocytopenia at 30 times MRHD. The anemia could be reversed upon discontinuation of dosing. Bone marrow suppression occurred to a varying degree, being associated only with dogs that died or were sacrificed in a moribund condition in the 1 year study. However, in the 47-week study at a dose 30 times MRHD, bone marrow suppression was found to be reversible upon continued drug administration.
Captopril caused hyperplasia of the juxtaglomerular apparatus of the kidneys at doses 7 to 200 times the MRDH in rats and mice, at 20 to 60 times MRHD in monkeys, and at 30 times the MRHD in dogs.
Gastric erosions/ulcerations were increased in incidence at 20 and 200 times MRHD in male rats and at 30 and 65 times MRHD in dogs and monkeys, respectively. Rabbits developed gastric and intestinal ulcers when given oral doses approximately 30 times MRHD for only five to seven days.
In the two-year rat study, irreversible and progressive variations in the caliber of retinal vessels (focal sacculations and constrictions) occurred at all dose levels (7 to 200 times MRHD) in a dose-related fashion. The effect was first observed in the 88^{th} week of dosing, with a progressively increased incidence thereafter, even after cessation of dosing.

Pregnancy Categories C (first trimester) and D (second and third trimesters)
See WARNINGS: Captopril, Fetal/Neonatal Morbidity and Mortality.

Pregnancy – Nonteratogenic Effects
Hydrochlorothiazide
Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers
Both captopril and hydrochlorothiazide are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from both drugs, a decision should be made whether to discontinue nursing or to discontinue therapy taking into account the importance of Captopril and Hydrochlorothiazide to the mother. (See PRECAUTIONS: Pediatric Use.)

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. There is limited experience reported in the literature with the use of captopril in the pediatric population; dosage, on a weight basis, was generally reported to be comparable to or less than that used in adults.
Infants, especially newborns, may be more susceptible to the adverse hemodynamic effects of captopril. Excessive, prolonged and unpredictable decreases in blood pressure and associated complications, including oliguria and seizures, have been reported. Captopril and Hydrochlorothiazide should be used in pediatric patients only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS

Captopril
Reported incidences are based on clinical trials involving approximately 7000 patients.

Renal
About one of 100 patients developed proteinuria (see WARNINGS).

Each of the following has been reported in approximately 1 to 2 of 1000 patients and are of uncertain relationship to drug use: renal insufficiency, renal failure, nephrotic syndrome, polyuria, oliguria, and urinary frequency.

Hematologic
Neutropenia/agranulocytosis has occurred (seeWARNINGS). Cases of anemia, thrombocytopenia, and pancytopenia have been reported.

Dermatologic
Rash, often with pruritus, and sometimes with fever, arthralgia, and eosinophilia, occurred in about 4 to 7 (depending on renal status and dose) of 100 patients, usually during the first four weeks of therapy. It is usually maculopapular, and rarely urticarial. The rash is usually mild and disappears within a few days of dosage reduction, short-term treatment with an antihistaminic agent, and/or discontinuing therapy; remission may occur even if captopril is continued. Pruritus, without rash, occurs in about 2 of 100 patients. Between 7 and 10 percent of patients with skin rash have shown eosinophilia and/or positive ANA titers. A reversible associated pemphigoid-like lesion, and photosensitivity, have also been reported.

Flushing or pallor has been reported in 2 to 5 of 1000 patients.

Cardiovascular
Hypotension may occur; see WARNINGS and PRECAUTIONS (Drug Interactions) for discussion of hypotension with captopril therapy.

Tachycardia, chest pain, and palpitations have each been observed in approximately 1 of 100 patients.

Angina pectoris, myocardial infarction, Raynaud’s syndrome, and congestive heart failure have each occurred in 2 to 3 of 1000 patients.

Dysgeusia
Approximately 2 to 4 (depending on renal status and dose) of 100 patients developed a diminution or loss of taste perception. Taste impairment is reversible and usually self-limited (2 to 3 months) even with continued drug administration. Weight loss may be associated with the loss of taste.

Angioedema
Angioedema involving the extremities, face, lips, mucous membranes, tongue, glottis or larynx has been reported in approximately one in 1000 patients. Angioedema involving the upper airways has caused fatal airway obstruction. (See WARNINGS: Captopril: Angioedema andPRECAUTIONS: Information for Patients).

Cough
Cough has been reported in 0.5 to 2 percent of patients treated with captopril in clinical trials (seePRECAUTIONS: General, Captopril, Cough).

The following have been reported in about 0.5 to 2 percent of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials: gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, alopecia, paresthesias.

Other clinical adverse effects reported since the drug was marketed are listed below by body system. In this setting, an incidence or causal relationship cannot be accurately determined.

Body as a whole
anaphylactoid reactions (see WARNINGS: Captopril: Anaphylactoid and possibly related reactions and PRECAUTIONS: Hemodialysis).

General
asthenia, gynecomastia.

Cardiovascular
cardiac arrest, cerebrovascular accident/insufficiency, rhythm disturbances, orthostatic hypotension, syncope.

Dermatologic
bullous pemphigus, erythema multiforme (including Stevens-Johnson syndrome), exfoliative dermatitis.

Gastrointestinal

pancreatitis, glossitis, dyspepsia.

Hematologic

anemia, including aplastic and hemolytic.

Hepatobilliary

jaundice, hepatitis, including rare cases of necrosis, cholestasis.

Metabolic

symptomatic hyponatremia.

Musculoskeletal

myalgia, myasthenia.

Nervous/Psychiatric

ataxia, confusion, depression, nervousness, somnolence.

Respiratory

bronchospasm, eosinophilic pneumonitis, rhinitis.

Special Senses

blurred vision.

Urogenital

impotence.

As with other ACE inhibitors, a syndrome has been reported which may include: fever, myalgia, arthralgia, interstitial nephritis, vasculitis, rash or other dermatologic manifestations, eosinophilia and an elevated ESR.

Fetal/Neonatal Morbidity and Mortality
See WARNINGS: Captopril, Fetal/Neonatal Morbidity and Mortality.

Hydrochlorothiazide

Gastrointestinal System
anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, and sialadenitis.

Central Nervous System
dizziness, vertigo, paresthesias, headache, and xanthopsia.

Hematologic
leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia, and hemolytic anemia.

Cardiovascular
orthostatic hypotension.

Hypersensitivity
purpura, photosensitivity, rash, urticaria, necrotizing angiitis (vasculitis; cutaneous vasculitis), fever, respiratory distress including pneumonitis, and anaphylactic reactions.

Other
hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, and transient blurred vision.

Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Altered Laboratory Findings

Serum Electrolytes
Hyperkalemia: small increases in serum potassium, especially in patients with renal impairment (seePRECAUTIONS: Captopril).

Hyponatremia
particularly in patients receiving a low sodium diet or concomitant diuretics.

BUN/Serum Creatinine
Transient elevations of BUN or serum creatinine especially in volume or salt depleted patients or those with renovascular hypertension may occur. Rapid reduction of longstanding or markedly elevated blood pressure can result in decreases in the glomerular filtration rate and, in turn, lead to increases in BUN or serum creatinine.

Hematologic
A positive ANA has been reported.

Liver Function Tests
Elevations of liver transaminases, alkaline phosphatase, and serum bilirubin have occurred.

OVERDOSAGE

Captopril
Correction of hypotension would be of primary concern. Volume expansion with an intravenous infusion of normal saline is the treatment of choice for restoration of blood pressure.
While captopril may be removed from the adult circulation by hemodialysis, there is inadequate data concerning the effectiveness of hemodialysis for removing it from the circulation of neonates or children. Peritoneal dialysis is not effective for removing captopril; there is no information concerning exchange transfusion for removing captopril from the general circulation.

Hydrochlorothiazide
In addition to the expected diuresis, overdosage of thiazides may produce varying degrees of lethargy which may progress to coma within a few hours, with minimal depression of respiration and cardiovascular function and without evidence of serum electrolyte changes or dehydration. The mechanism of thiazide-induced CNS depression is unknown. Gastrointestinal irritation and hypermotility may occur. Transitory increase in BUN has been reported, and serum electrolyte changes may occur, especially in patients with impaired renal function.
In addition to gastric lavage and supportive therapy for stupor or coma, symptomatic treatment of gastrointestinal effects may be needed. The degree to which hydrochlorothiazide is removed by hemodialysis has not been clearly established. Measures as required to maintain hydration, electrolyte balance, respiration, and cardiovascular and renal function should be instituted.

DOSAGE AND ADMINISTRATION
DOSAGE MUST BE INDIVIDUALIZED ACCORDING TO PATIENT'S RESPONSE.
Captopril and Hydrochlorothiazide tablets may be substituted for the previously titrated individual components.
Alternatively, therapy may be instituted with a single tablet of Captopril and Hydrochlorothiazide 25 mg/15 mg taken once daily.
For patients insufficiently responsive to the initial dose, additional captopril or hydrochlorothiazide may be added as individual

components or by using Captopril and Hydrochlorothiazide tablets 50 mg/15 mg, 25 mg/25 mg or 50 mg/25 mg, or divided doses may be used.
Because the full effect of a given dose may not be attained for 6 to 8 weeks, dosage adjustments should generally be made at 6 week intervals, unless the clinical situation demands more rapid adjustment.
In general, daily doses of captopril should not exceed 150 mg and of hydrochlorothiazide should not exceed 50 mg.
Captopril and Hydrochlorothiazide tablets should be taken one hour before meals.

Dosage Adjustment in Renal Impairment
Because captopril and hydrochlorothiazide are excreted primarily by the kidneys, excretion rates are reduced in patients with impaired renal function. These patients will take longer to reach steady-state captopril levels and will reach higher steady-state levels for a given daily dose than patients with normal renal function. Therefore, these patients may respond to smaller or less frequent doses of Captopril and Hydrochlorothiazide tablets.
After the desired therapeutic effect has been achieved, the dose intervals should be increased or the total daily dose reduced until the minimal effective dose is achieved. When concomitant diuretic therapy is required in patients with severe renal impairment, a loop diuretic (e.g., furosemide), rather than a thiazide diuretic is preferred for use with captopril; therefore, for patients with severe renal dysfunction the captopril-hydrochlorothiazide combination tablet is not usually recommended (See WARNINGS: Captopril: Anaphylactoid reactions during membrane exposure and PRECAUTIONS: Hemodialysis).

HOW SUPPLIED
Captopril and Hydrochlorothiazide Tablets, USP are supplied as follows:
25 mg/15 mg – white, round tablets, debossed with“Endo” and “733” on one side and quadrisected on the other.
Bottles of 100 NDC 60951-733-70
25 mg/25 mg – peach, round tablets, debossed with “Endo” and “741” on one side and quadrisected on the other.
Bottles of 100 NDC 60951-741-70
50 mg/15 mg – white, round tablets, debossed with “Endo” and “739” on one side and bisected on the other.
Bottles of 100 NDC 60951-739-70
50 mg/25 mg – peach round tablets, debossed with “Endo” and “731” on one side and bisected on the other.
Bottles of 100 NDC 60951-731-70
Store at controlled room temperature, 15°-30°C (59°-86°F). Dispense in a tight container as defined in the USP. Protect from moisture. Keep bottles tightly closed.
Caution: Federal (USA) law prohibits dispensing without prescription.
Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, Pennsylvania 19317
Manufactured by:
DuPont Pharma
Wilmington, Delaware 19880
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